Cell Metabolism
Previews

NCOA5, IL-6, Type 2 Diabetes, and HCC: The Deadly Quartet

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Although type 2 diabetes (T2D) is an established risk factor for hepatocellular carcinoma (HCC), the underlying mechanism that connects these two diseases is unknown. Gao et al. (2013) now suggest that nuclear receptor coactivator 5 (NCOA5) provides a genetic link between the two diseases through its effects on hepatic IL-6 expression.

Diabetes, obesity, and male gender are associated with elevated HCC risk (El-Serag and Rudolph, 2007; Naugler et al., 2007). Given the increasing prevalence of obesity and T2D, it is important to understand the underlying mechanisms linking them to HCC development. Although previous work had implicated inflammation in the pathogenesis of both T2D and HCC (Donath and Shoelson, 2011; He and Karin, 2011), the precise molecular link between the two remains unknown. Proinflammatory cytokines such as TNF and IL-6 are involved in both HCC and T2D. But whereas the tumor promoting role of IL-6 in HCC is quite clear (He et al., 2013), its involvement in the pathogenesis of T2D depends on whether it is produced acutely or chronically. Nonetheless, as far as the liver is concerned, it is widely accepted that chronically elevated IL-6 promotes hepatic insulin resistance. Now the question arises: does IL-6 link T2D to HCC? A recent study (Gao et al., 2013) provides some support to this hypothesis by showing that haploinsufficiency of NCOA5, a transcriptional regulator that suppresses IL-6 expression, predisposes mice to insulin resistance, T2D, and HCC.

NCOA5, also known as coactivator independent of AF2 (CIA), is a coregulator of estrogen receptor α (ERα)-mediated transcription, which influences both HCC and T2D (Naugler et al., 2007; Tiano et al., 2011). Moreover, *NCOA5* was recently identified as a T2D susceptibility gene (Lewis et al., 2010). In the new study, *Ncoa5*$^{+/-}$ (haploinsufficient) male mice were generated in two different genetic backgrounds (due to fertility issues, homozygous *Ncoa5*$^{-/-}$ mice were not studied) and found to develop HCC by 18 months of age. Additionally, *Ncoa5*$^{+/-}$ male mice became insulin resistant at a young age and presented with elevated fasting blood glucose compared to wild-type (WT) counterparts. Insulin signaling analysis showed that insulin-induced phosphorylation of insulin receptor (IR-β), insulin receptor substrate-1 (IRS-1), and AKT is impaired in *Ncoa5*$^{+/-}$ male liver (Figure 1). *Ncoa5*$^{+/-}$ mice also failed to undergo a compensatory increase in β cell mass and insulin secretion, suggesting this process is also impaired. Older (6–10 months) *Ncoa5*$^{+/-}$ males showed liver inflammation, steatosis, fibrosis, and dysplasia. Serum alanine aminotransferase, α-fetoprotein, and hepatic triglycerides were elevated relative to WT mice. Moreover, the *Ncoa5*$^{+/-}$ liver exhibited more cell death and compensatory proliferation, a key driver of hepatocarcinogenesis (Maeda et al., 2005). Hepatic IL-6 and TNF were elevated, too, mostly due to increased production by liver myeloid cells. Although NCOA5 directly regulates *IL-6* gene transcription, other hepatocyte-specific targets for NCOA5 that are involved in HCC development cannot be ruled out, and future studies should include cell type-specific *Ncoa5* gene disruption. The authors also demonstrated an effect of NCAO5 on *IL-6* gene expression in a human macrophage cell line, confirming that this pathway is not species specific. Increased IL-6 expression in *Ncoa5*$^{+/-}$ mouse liver resulted in activation of STAT3 and SOCS3, which negatively modulate insulin signaling. The current study suggests that chronic activation of IL-6-STAT3 signaling promotes insulin resistance in *Ncoa5*$^{+/-}$ mice (Figure 1).

How does NCOA5 regulate IL-6 expression? NCOA5 is a coactivator for ERα, and activated ERα interferes with NF-κB-mediated *IL-6* gene transcription (Naugler et al., 2007). Quantitative chromatin immunoprecipitation (qChIP) in mouse macrophage cells indicated increased NCOA5 and ERα recruitment to the *IL-6* promoter upon estrogen stimulation, and a reporter gene assay showed that NCOA5 represses LPS-induced NF-κB-mediated *IL-6* promoter activity. Correspondingly, qChIP demonstrated increased RNA Pol II recruitment to the *IL-6* promoter in *Ncoa5*$^{+/-}$ livers. Therefore, NCOA5 haploinsufficiency increases *IL-6* gene transcription by interfering with ERα-mediated repression.

To validate whether increased IL-6 expression is the main trigger for the pathologies observed in *Ncoa5*$^{+/-}$ mice, the authors generated *Ncoa5*$^{+/-}$*Il-6*$^{+/-}$ mice, which express 50% less IL-6 than *Ncoa5*$^{+/-}$*Il-6*$^{+/+}$ mice. Reduced IL-6 expression significantly improved fasting blood glucose and insulin resistance. Heterozygous *IL-6* deletion, however, was unable to block HCC development, but it did reduce tumor load. These findings are consistent with previous observations that ERα activation attenuates chemically induced HCC development (Naugler et al., 2007) and that IL-6 ablation blocks HCC development (He et al., 2013).

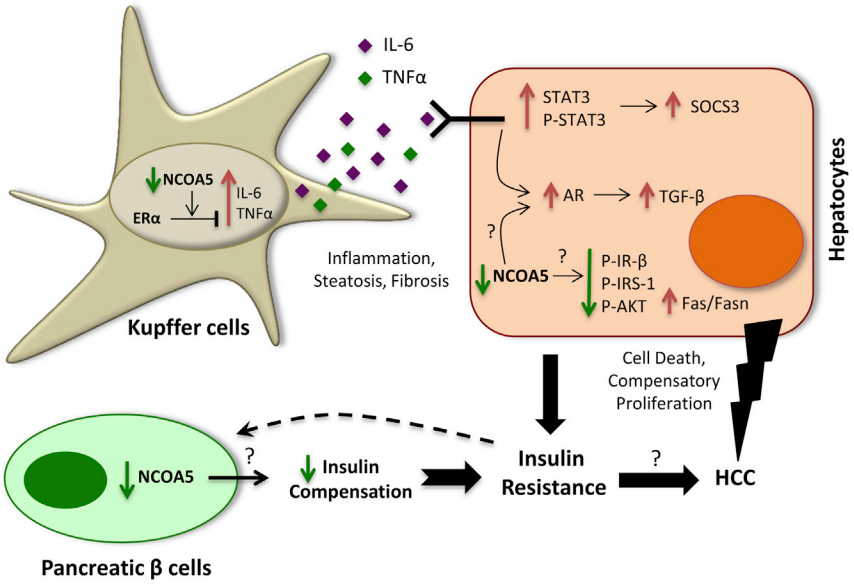

Figure 1. NCOA5 Haploinsufficiency Promotes Hepatic Inflammation, Insulin Resistance, and HCC Development

Reduced NCOA5 expression induces insulin resistance by interfering with insulin signaling in the liver as well as by interfering with insulin production by pancreatic β cells. NCOA5 haploinsufficiency creates a protumorigenic microenvironment in the liver that results in HCC development, which partly depends on IL-6 overexpression by Kupffer cells. NCOA5 is also involved in ERα-mediated suppression of *IL-6*.

Although IL-6 plays a pivotal role in the different pathologies exhibited by *Ncoa5*$^{+/-}$ mice, Gao et al. investigated whether other factors are also involved. They found that androgen receptor (AR), fatty acid synthase (FAS), and TGF-β are negatively regulated by NCOA5 (Figure 1). Therefore, in *Ncoa5*$^{+/-}$ mice, these factors are overexpressed and may contribute to the pathogenesis of T2D and HCC. Previous studies have shown that both AR (Naugler et al., 2007) and TGF-β (Yang et al., 2013) signals contribute to HCC development.

Lastly, Gao et al. analyzed human HCC and found that NCOA5 expression was significantly reduced in 40% of tumors compared to the adjacent nontumor area. In general, when compared to a normal liver, there is a trend of reduced NCOA5 expression even in the nontumor area (63%) of HCC-bearing livers. Interestingly, sequencing studies revealed an alternatively spliced isoform of *NCOA5* mRNA, encoding a truncated protein that lacks the transcriptional activation domain, s-NCOA5, whose expression is elevated in 43% of HCC samples compared to the adjacent nontumor area, indicating an inverse correlation with full-length NCOA5 expression.

Together these results suggest NCOA5 deficiency as a possible link between T2D and HCC. However, it is not clear whether obesity-induced T2D has any effect on NCOA5 expression and whether NCOA5 deficiency contributes to HCC development in patients suffering from nonalcoholic steatohepatitis (NASH), most of whom are diabetic. Clearly, more studies are needed to determine whether environmental and dietary factors modulate NCOA5 expression, thereby influencing T2D and HCC pathogenesis. Future studies should also address the role of NCAO5 in pancreatic β cell function, hepatic glucose production, as well as its role in insulin signaling in adipocytes and skeletal muscle. Additional studies with larger cohorts of patients with T2D, HCC, and HCC with comorbid T2D are needed to determine whether *NCOA5* mutations or reduced expression in liver and pancreas predispose to either or both pathologies. This study is important because it reinforces the inflammation- and IL-6-based link between T2D and HCC, suggesting that modulation of ERα signaling may be used for the prevention and/or treatment of these common pathologies of the modern era.

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